

'Acidic gut syndrome': is it a problem for animals and humans?

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Summary

Acid accumulation in the gut occurs when a number of dietary factors and animal digestive responses interact to deliver readily fermentable carbohydrate to parts of the digestive tract colonised by bacteria capable of rapid fermentation and multiplication. Lactic acidosis is a well documented condition characterised by the absorption of lactic acid from the rumen or hind gut, the slow metabolism of D-lactic acid, and the effect of these processes on the acid-base balance in the animal's tissues. It is suggested that a new condition, 'acidic gut syndrome' (AGS) should be recognised. This is characterised by the accumulation of acid in the gut at concentrations that have not previously been considered harmful to animals or humans. The detrimental effects initiated by lactic acid and low pH may be mediated through direct action on the gut wall, through the production of bacterial endotoxin, through the combination of acid and endotoxins or through other factors. The adverse effects associated with AGS are not conclusively defined but may include behavioural changes, increased risk of gut infections, skin and respiratory conditions and a range of other problems which have traditionally been attributed to food allergies or reactions to stress. It is likely that acidic gut syndrome acts through the immune system and in this way may form a basis for understanding a range of secondary diseases of previously unknown origin. These factors are discussed to highlight the possibility of acid accumulation in the gut of at least a proportion of animals and humans, under a wide range of dietary conditions. Acute lactic acidosis is still acknowledged as a serious problem in extreme circumstances, but it is possible that acidic gut syndrome may be more common and that it may affect production, health and welfare in significant ways.

Introduction

A number of dietary and animal digestive factors interact to influence the possibility of acid accumulation in those

parts of the digestive tract adapted for microbial fermentation where the normal pH is between 6.5 and 7.0. The problem of lactic acidosis is widely recognised in ruminants and although it is largely attributed to the fermentation of starch and sugars in the rumen, it is also a significant problem in the hind gut (Lee *et al.* 1982; Godfrey *et al.* 1992). Hind gut acidosis is also well recognised in horses where this condition is closely related to founder or laminitis (Garner *et al.* 1987; Rowe *et al.* 1994). The pathogenesis of lactic acidosis, or D-lactic acidosis, is described as a good example of metabolic acidosis in which considerable amounts of lactic acid are . . . 'absorbed through the wall of the rumen and some undoubtedly moves into and is absorbed from the intestinal tract' (Blood *et al.* 1983). D-lactic acid is more slowly metabolized than L-lactic acid and therefore accumulates in the tissues where it causes severe D-lactic acidosis. These authors suggest that endotoxins released with the death of gram-negative bacteria in the gut may play a role in the pathogenesis of lactic acidosis. Acidic gut syndrome on the other hand does not depend on metabolic acidosis as a primary or secondary factor in its pathogenesis but rather on acidity within the gut. The adverse toxic effects may be mediated through the direct effect of acid on the gut wall, or through microbial endotoxins, through the combination of both acidity and endotoxins, or through some other factor, initiated within the gut or gut wall, and acting systemically.

Conditions which may be associated with acidic gut syndrome

A recent study on adverse behavioural changes in the horse, in response to increasing levels of grain in the diet, showed that the frequency of unusual behavioural activities was closely related to faecal pH. Within the range of pH 7 to pH 6, which has traditionally been

considered to be quite normal, the more acidic the faeces, the higher the frequency of adverse behaviour (see Figure 1 from Johnson *et al.* 1997). It is possible that some behavioural changes in humans linked to certain foods and food intolerances may also be associated with fermentation of carbohydrates and accumulation of acid in the gut. In addition, the recent work by Pethick and his colleagues (Pluske *et al.* 1997) has identified hind gut fermentation and acidity as a primary facilitating factor in the development of *Serpulina* infection (swine dysentery).

There is also good circumstantial evidence for other disease conditions being linked to acidic gut syndrome. These conditions are mainly associated with high levels of grain feeding and circumstances where there is a well-recognised risk of lactic acidosis but a low incidence of the frank disease condition. For example there are numerous health problems in feedlot cattle which occur during the first few weeks in the feed lot when animals are adapting to diets based on cereal grain. These include respiratory diseases, an uneven pattern of eating and lactic acidosis. Although lactic acid in the rumen at time of death has not been found to be closely related to respiratory or other diseases which occur during this period of grain introduction, it is possible that this is because of the transitory nature of acid accumulation following carbohydrate overload. A more sensitive assessment of acid accumulation, at least in the gut, could be the pH of faeces that would allow investigation of the possible link between gut acidity

and secondary disease problems. Currently there appears to be no data relating faecal pH to other feed lot disease conditions occurring during the first few weeks of adaptation to grain-based diets. The high incidence of diarrhoea in feed lot cattle, and the low faecal pH of cattle on grain-based diets, suggests that acid accumulation in the hind gut could be widespread and it is possible that it is a predisposing factor for the development of secondary disease problems. In high-producing dairy cattle lameness is now recognised as the second most important disease problem after mastitis (Esslemont and Kossaibati, 1996). While the incidence of chronic lameness in dairy cattle has been linked to the use of grain-based supplements it has not been directly associated with lactic acidosis (Bess and Whittier, 1996). It is likely that acidic gut syndrome is not confined to those animal species, ruminants and horses, in which acute lactic acidosis has been well documented as a major problem in relation to production and welfare. Hind gut acid accumulation is not yet recognised as a problem in monogastric animals such as pigs and poultry. In these species it is assumed that hind gut fermentation of 'fibrous residues' causes no problems to the animal other than some 'osmotic diarrhoea' or wet droppings. There are, however, significant problems of lameness in intensively housed pigs. While this lameness is mainly attributed to the concrete floors and hard surfaces in the housing, it is a condition not unlike lameness in dairy cattle and horses fed on high grain diets. One can also speculate that some of the behavioural problems such as tail biting in pigs, and vent pecking in poultry may be related to hind gut acid accumulation in the same way as 'bored' behavioural changes are related to low faecal pH in the horse (Johnson *et al.* 1997).

Although it is recognised that some 'food allergies' and 'food intolerances' in humans and dogs may cause 'osmotic diarrhoea', the low pH of the faeces in these situations has been regarded as a side effect and has not attracted any attention as a possible primary cause of adverse secondary effects. It is, however, possible that the low gut pH and bacterial endotoxins associated with increased acidity during 'osmotic' diarrhoea could be primary agents mediating the 'allergic reaction' rather than being just other side effects. A number of studies on the malabsorption of carbohydrate in dogs and humans report 'osmotic diarrhoea' associated with faecal pH below 5.0 (e.g. Holtug *et al.* 1992). There is little information available on the relationship between irritable bowel syndrome and faecal pH and it would be interesting to know if this condition is associated with accumulation of acid in the gut under some circumstances. With reference to data summarised in Figure 1, as well as data described above, it is clear that these levels of acidity associated with 'osmotic diarrhoea' are high enough to initiate adverse secondary effects through direct effects on the gut or through production of microbial endotoxins.

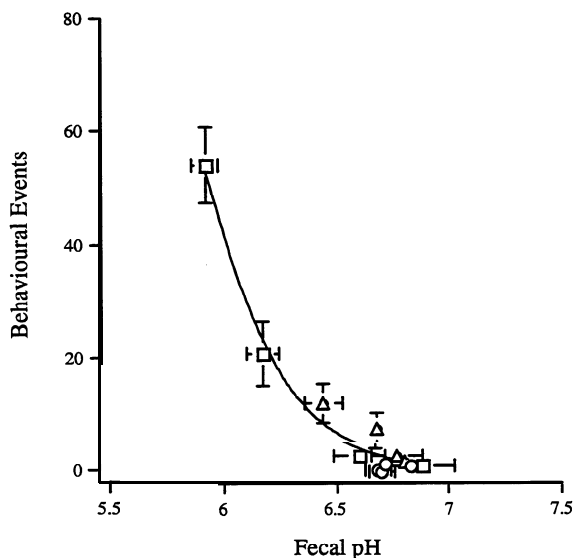


Figure 1 Relationship between faecal pH and behavioural events (eating bedding, grasping, wood chewing and stall licking). Each point represents the weekly sum of observations for 2 hours every day of the week. Horses were fed increasing levels of grain over a 4 week period and differences in faecal acid were related to grain with or without virginiamycin and Foudnerguard™. There was no effect of time in relation to the development of behavioural patterns (from Johnson *et al.* 1997).

Gut acidity-why are lactic acid and endotoxins important?

Lactic acid

Under normal conditions of fermentation in the **rumen** and/or the hind gut, lactic acid is not present in measurable amounts even though it can be a very important intermediate in the production of propionic acid. Similarly, when significant quantities of lactic acid are consumed in the diet (e.g. silages in which over 13% of the dry matter can be lactic acid) no lactic acid is measurable in the **rumen** as it is rapidly converted to VFA (mainly acetate and propionate) (Gill *et al.* 1986). The conversion of lactic acid to propionate is thermodynamically favourable for microbes and this process is normally rapid and complete. The accumulation of lactic acid only occurs when the bacteria responsible for the conversion of lactic acid to VFA are not functioning efficiently or are not present in sufficient numbers to cope with the amount of lactic acid being produced. This occurs when there is a build up of VFA and a reduced pH. The lactic acid-utilizing bacteria are far more sensitive to low pH than the lactic acid producers and once the balance is upset the situation is exacerbated by further accumulation of lactic acid which results in even lower pH (Schwartz and Gilchrist, 1974). A recent study by Ding *et al.* (1997) has shown that there is no absorption of lactic acid **from the rumen** or caecum in sheep in the absence of acute carbohydrate overload (Figure 2). This means that any net production of lactic acid in the **rumen** or caecum will lead to an accumulation of acid that will lower pH. It is possible that this same disparity between VFA and lactic acid absorption occurs in the hind gut of monogastric animals and contributes to acidic gut contents in these species in the same way as it does in ruminants.

It therefore appears that the accumulation of lactic acid is always associated with low pH and also signals the failure of the gram-negative lactate utilisers. An example of the role of lactate in the accumulation of acid

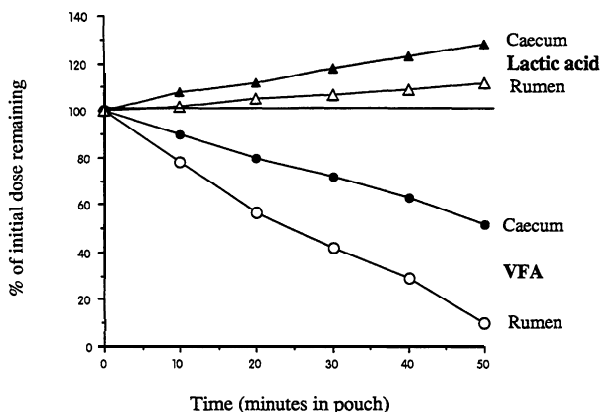


Figure 2 Apparent absorption of test solutions of acids from surgically sealed pouches in the rumen and caecum in the sheep. The apparent increase in lactic acid was due to conversion from VFA and/or tissue synthesis (From Ding *et al.* 1997).

in the gut which demonstrates the relationship between lactic acid and pH is shown in Figure 3. The main lactic acid utilisers are gram-negative bacteria whereas the bacteria primarily involved in lactic acid production, ***Streptococcus bovis*** and ***Lactobacillus spp.***, are gram-positive (Schwartz and Gilchrist, 1974). Accumulation of lactic acid under these conditions is therefore likely to have a dual significance in contributing a non-absorbable acid to the gut contents and as an indicator of a decline in gram-negative bacteria which is almost certainly linked with bacterial endotoxin lipopolysaccharide release.

Endotoxins

Endotoxins (lipopolysaccharides, LPS) are released during lysis of **gram-negative** bacteria. LPS release can occur during the sudden decrease in pH associated with rapid fermentation of carbohydrate and has been demonstrated in the **rumen** of sheep (Dougherty *et al.* 1975) and the caecum of horses (Moore *et al.* 1979). The results of Moore *et al.* (1979) (Figure 4) show that although there is a tendency towards higher levels of endotoxin accumulation at lower pH, considerable quantities of endotoxins can be released without the pH falling below 6.0. Studies by Hood and Stephens (1981) and by Mullenax *et al.* (1966) suggest that under 'normal' conditions in the **rumen** and caecum (without acute lactic acidosis) little absorption of endotoxin **from the gut** is likely to occur. When Hood and Stephens (1981) administered bacterial endotoxin into the hind gut of horses, there was no development of laminitis and they concluded that there was no absorption of the endotoxin. Similar studies in ruminants indicated different responses to endotoxins administered intraruminally and intravenously, even when the endotoxin was administered intraruminally with lactic acid (Mullenax *et al.* 1966).

On the other hand, under conditions of acute lactic acidosis gross structural changes to the **rumen** wall in sheep (Lee *et al.* 1982) and to the caecal wall in horses

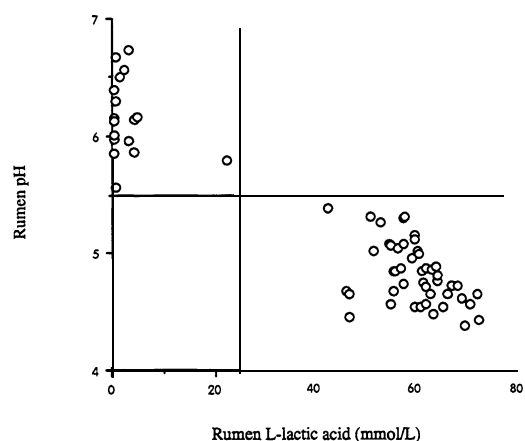


Figure 3 Relationship between lactic acid concentration and rumen pH. This suggests that when lactic acid is present in the rumen at concentrations of over 20 mmol/L the pH will normally be below 5.5.

(Krueger *et al.* 1986) may make it possible for both bacterial endotoxins and lactic acid to gain access to the vascular system. It is clear that both lactic acid and endotoxins can be absorbed from the gut during acute lactic acidosis (Godfrey *et al.* 1995; Table 1, Dougherty *et al.* 1975 and Sprouse *et al.* 1987) However, this situation is clearly different from acidic gut syndrome. The results from the two studies by Godfrey *et al.* (1992 and 1995) given in Table 1 indicate that significant absorption of lactic acid (and presumably endotoxins as well) only occurs under extreme conditions of fermentative acidosis in the gut (Godfrey *et al.* 1995). With lower levels of lactic acid and higher pH in the gut (Godfrey, 1992), there was very little absorption of lactic acid from the gut. This is seen as the difference between the ratio of D- and L- lactate in the gut and in the blood. There are always measurable amounts of L- lactate in the blood from tissue metabolism and if lactic acid from the gut makes a major contribution to blood lactic acid, the ratio of D-lactate to L-lactate should approach that measured in the main fermentation compartments in the gut.

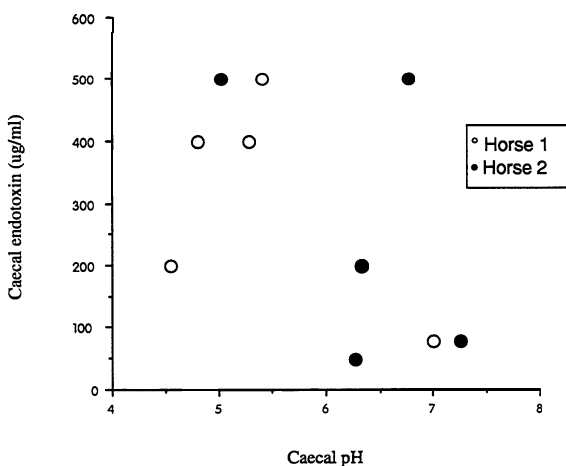


Figure 4 Endotoxin levels in relation to pH in the caecum of two horses measured following carbohydrate overload (Moore *et al.* 1979).

The bacterial endotoxins also stimulate tumour necrosis factor (TNF) which can initiate the cytokine cascade, releasing IL-1, IL-6 and IL-8 (Abbas *et al.* 1996). The effects of these cytokines can be **widespread**—acting both locally and systemically depending on the levels present (Tracey *et al.* 1989)—and this is summarised in Figure 5. Pollitt (1996) reported a range of histological changes in the hooves of horses following carbohydrate overload and also the development of laminitis, both of which were consistent with cytokine activity. In the case of hoof damage at the **lamellar** level, Pollitt (1996) suggests there may be specific involvement of **metallo-proteases**, but there is a sufficiently wide range of cytokine-initiated activities to explain damage and activation of other tissue types.

When is acidic gut syndrome likely to be a problem?

The factors that have the potential to contribute to the risk of lactic acid build up in the gut are numerous and are considered below in terms of dietary and animal digestive factors. They include any input or change which contributes to an increased supply of fermentable carbohydrate to any part of the digestive tract containing a dense bacterial population (i.e. fore stomach or hind gut). Since a range of animal and feed factors affect the risk of acid accumulation in the gut, it is not surprising that there is significant variation between individual animals in the way in which they respond to similar quantities of dietary grain or other forms of fermentable carbohydrate. This variation is illustrated in Figure 6 and highlights the fact that problems associated with acid accumulation should be considered in terms of the proportion of animals affected and the severity of the problem for those individuals. From this perspective it is appropriate to consider different management strategies for more susceptible individuals and/or for

Table 1 L- and D-lactate concentrations (mmol/L) in the rumen, caecum and blood of sheep following consumption of cereal grain. (From ¹ Godfrey *et al.* 1992 and ² Godfrey *et al.* 1995).

Time after grain feeding:	Rumen	Caecum	Plasma		Reference
	24 h	24 h	24 h	48 h	
pH	5.28	6.10			1
L-lactate	19.3	10.5	2.37		1
D-lactate	15.4	8.2	0.19		1
L- to D- ratio (L-lactate/D-lactate)	1.24	1.28	12.4		1
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pH	4.72				2
L-lactate	62.8		2.38	1.73	2
D-lactate	36.4		2.89	7.04	2
L- to D- ratio (L-lactate/D-lactate)	1.72		0.82	0.25	2

dietary regimes which are likely to be associated with higher risks of gut acid accumulation. The challenge we face to make this approach to be practical and useful is to **first** understand the condition more clearly so that those individuals and diets which carry the greatest risk can be easily identified and appropriately managed.

Dietary factors

Dietary characteristics associated with an increased risk of fermentative acidosis are summarised as follows:

Source of carbohydrate is important as there are major differences between grains in terms of the structure and characteristics of starch granules as well as the content of non-starch polysaccharides (NSP). Differences between the major grains are summarised in Table 2. Starch, which is soluble and readily fermented such as that in wheat, poses the greatest risk for forestomach fermenters such as ruminants. Resistance of starch to intestinal digestion increases the risk of greater hind gut fermentation and acid accumulation in the caecum

Table 2 Characteristics of different grains in terms of fermentation and digestion in the ruminant and of non-starch polysaccharides and digestion in poultry. (from 'Rowe and Pethick, 1994'; from Choct and Annison, 1990).

	Maize	Sorghum	Barley	Wheat	Oats
Solubility of dry matter (nylon bags) ¹	26	32	54	68	96
For each kg DM consumed ¹					
Starch intake (g/d)	760	750	610	760	420
Starch fermented in rumen (g/d)	578	480	531	676	386
Starch digested post ruminally (g/d)	120	169	58	71	26
Starch excreted in faeces (g/d)	57	97	40	14	7
NSP ² (g/kg)	3.9	2.6	10.8	6.0	
ME in poultry ² (MJ/kg)	16.0	16.0	12.1	14.2	

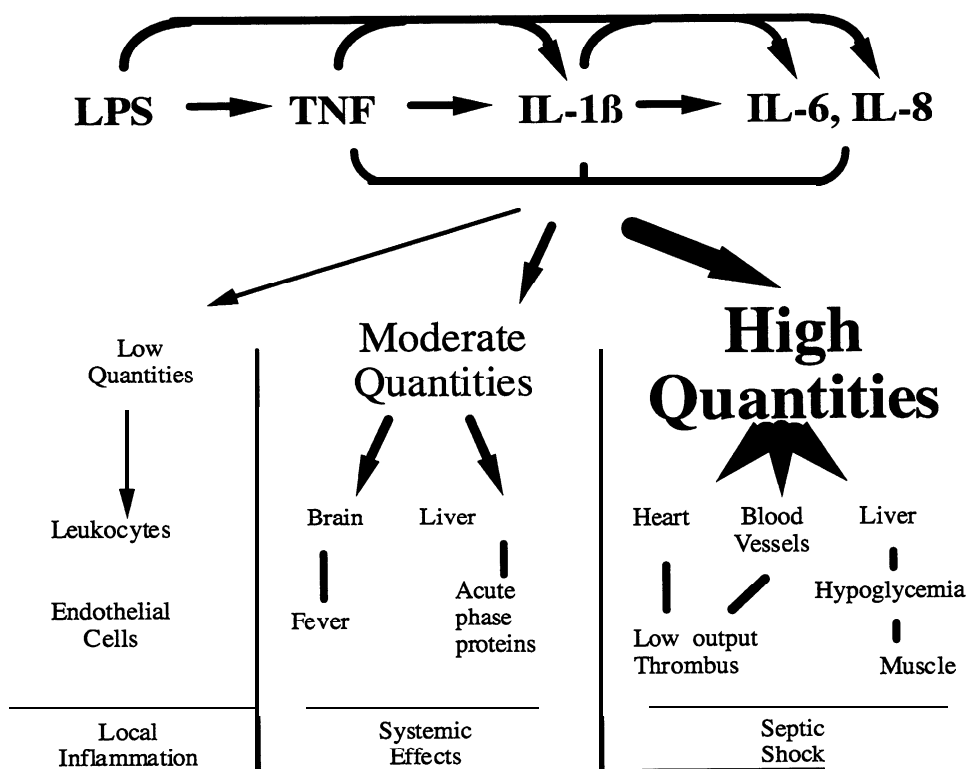


Figure 5 Summary of the range of effects which varying levels of cytokine responses can have locally and systemically when stimulated by bacterial lipopolysaccharide (LPS) endotoxin. Other abbreviations: TNF, Tumour necrosis factor; IL, interleukin (adapted from Abb1919as *et al.* 96). While this model is based on systemic infection it is likely that the endotoxin (LPS), released with the death of gram -ve bacteria in the gut under acidic conditions triggers local and systemic cytokine effects.

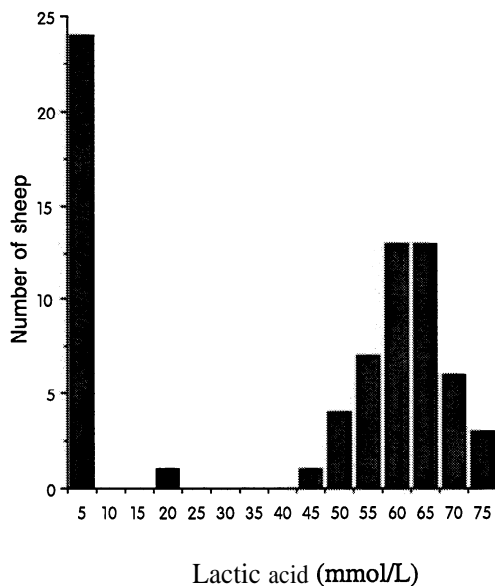


Figure 6 Variation in the concentration of lactic acid in rumen fluid of sheep 24 h after they were given 800 g of ground wheat via stomach tube. The number shown for 5 mmol/L is the total number of animals with concentrations of lactic acid between 0 and 5 mmol/L. The numbers of sheep for 20, 45 etc is the total with rumen lactate concentrations ± 2.5 mmol/L either side of the figure shown (J.B. Rowe, E.M. Aitchison and C.L. McDonald, unpublished).

and colon. The NSP fraction is highly fermentable and generates acid production in the hind gut. NSP can also reduce starch digestion through increasing the viscosity of the digesta and in this way may act synergistically with the starch fraction to increase hind gut fermentation. Although the importance of NSP is well recognised in monogastric nutrition, there has been little research on their effect in ruminant animals.

Age (storage) of grain—reduces the endogenous enzyme and NSP contents of the grain and can have a significant effect in improving intestinal digestion of carbohydrate (Choct and Hughes, 1997). This helps to explain why a sudden change to ‘new season’ grain can cause production problems associated with reduced intestinal digestion and increased hind gut fermentation and faecal output.

Processing of the dietary ingredients affects particle size, solubility, gelatinisation and the rate at which it can be ingested. Any treatment which decreases particle size, reduces the ‘resistance of starch to digestion or increases its solubility will increase the rate of rumen fermentation and gastric digestion and reduce the amount of fermentable carbohydrate passing to the hind gut. The use of exogenous enzymes that are active against starch and NSP are increasingly used in monogastric and ruminant nutrition. They have the ability to improve the extent and to alter the site of digestion. One side effect of enzymes active against NSP is their potential to increase the rate and extent of fermentation in the hind gut (Choct *et al.* 1996).

Frequency of feeding and meal size—determine the amount of fermentable substrate delivered for fermentation in the rumen to the stomach for acid digestion. Large amounts of carbohydrate ingested once or twice per day, or twice per week in the case of grain supplements for grazing ruminants, can overload the forestomachs and lead to acid accumulation in the rumen. It can also result in incomplete gastric digestion and an increased fermentation in the hind gut. Among the human population ‘fast food’ consumption is often rapid. Factors which facilitate rapid ingestion of carbohydrate are likely to result in less intestinal digestion and more hind gut fermentation. There is often not enough time for regular meals and there may be one large meal per day with a couple of light snacks at other times and this pattern of intake could result in more carbohydrate passing to the hind gut.

Animal and human factors

Efficiency of mastication—and the size of the digestive tract affect the particle size of feeds which in turn influence the site of digestion or fermentation. There are important differences between species in terms of mastication and in the size of particles which pass from one digestive compartment to another. There are also differences between individuals and changes with age and dentition which can have a marked effect on size of particles and the rate at which they enter different parts of the digestive tract.

Turn over rate and residence time-of material in the rumen has a significant effect on the extent of fermentation in that organ and the amount of undigested carbohydrate passing to the small intestines. Rate of passage also has an important role in determining site of digestion and is influenced by hormonal and other systemic factors such as stress cold weather and enteritis. It is also influenced by the autonomic nervous system, disease states, drug exposure and nature of the diet. When material passes through the small intestine more quickly there may be less complete digestion of carbohydrate. The rate of passage is also important in monogastric animals and influences intestinal digestion and hind gut fermentation.

Adaptation of the bacterial population-for starch fermentation and lactic acid utilization forms the basis of all practical grain feeding programs for ruminant animals. A gradual increase in the amount of grain allows a build up of bacteria able to convert lactic acid to VFA. This is not only important in terms of preventing lactic acid accumulation and low pH but also from the point of view of the stability of the gram-negative population of bacteria which utilise lactic acid. If this population declines sharply in response to increased acidity, and if there is a rapid expansion of the gram-positive population of bacteria which produce lactic acid, there will almost certainly be a release of endotoxins which are likely to be very important in acidic gut syndrome.

Enzyme activity-in the gastro-intestinal tract affects the extent of carbohydrate digestion as well as the range of substrates degraded and absorbed. It is likely that there are significant differences between species in endogenous enzyme activity and the efficiency of **gastro-intestinal** digestion and absorption of starch and sugars. For example, poultry digest around 99% of the starch content of ground sorghum grain (Choct and Annison, 1990) whereas cattle can excrete up to 25% of sorghum starch undigested in the faeces. There are also marked differences between individuals in enzyme activity which can have an important effect on site of digestion and the accumulation of acid in the gut. Gross enzyme deficiencies are recognised in humans in terms of 'malabsorption' of carbohydrate and food intolerances.

Intestinal adaptation—to the digestion and absorption of various carbohydrate fractions has an important effect on the site of carbohydrate digestion and on the potential for increased hind gut fermentation. Data in the dog suggest that absorption of carbohydrate can be increased up to six-fold through adaptation (Meyer and Kienzle, 1991 quoted by Maskell and Johnson, 1993). The requirement for digestive adaptation to different carbohydrates is important in animal production where health problems are often encountered when animals are changed from one type of grain to another. Adaptation is also likely to be important in the human population for whom modern diets contain far more variety in terms of sources of carbohydrate and in types of preparation and patterns of consumption. There are also a number of new carbohydrates in the form of modified starches, used as thickeners. A high amylose starch has also been introduced which is known to have a low level of intestinal digestion and readily fermentable in the hind gut.

Salivary secretion-is an important source of enzymes and buffers. The amount of saliva secreted and its composition is likely to vary between individuals. In sheep and cattle, saliva provides buffering capacity in the rumen. In monogastric animals, variation is more likely to be important in terms of enzyme activity and the effect that this will have on efficiency of digestion prior to hind gut fermentation.

Rate of volatile fatty acids (VFA) absorption-it is unclear whether there are major differences between animals in the rate at which VFA are absorbed from the rumen or the hind gut. As well as differences between species in the rate of acid absorption from various parts of the tract, it is possible that variation also occurs between individuals and may also be sensitive to hormonal control and/or age.

The range of dietary and animal/human factors summarised above highlights many areas of rising risk associated with our increasingly intensive methods of livestock production and our own dietary habits. A number of the major intensive animal production

diseases and the **allergic/autoimmune** conditions in humans are without known cause or defined aetiology. At the same time, there are clear trends in animal production as well as in the Western human diet towards the inclusion of more grain, a greater variety of grains and new methods of processing grains and starches. In the human diet there has been a marked increase in the intake of pasta and high 'fibre' carbohydrates designed and selected to reduce intestinal digestion and increase hind gut fermentation. Processed starches are also increasingly used as thickeners, replacing fat or eggs. In beef production there has been a dramatic increase in the use of cereal grain in feed lots and in the dairy industry grain is now widely used to maximise milk yield per cow. These increases in the consumption of carbohydrates in humans and animals have coincided with the use of probiotics to increase lactic acid production in the gut. Their use is based on the theory that a healthy population of gram-positive lactic acid producers (*Lactobacillus* and others) will exclude gram-negative pathogens from the gut (see Brown and McNaught, 1997). Because the potential risk of acidic gut syndrome has not yet been recognised, there has been no attention to the potentially dangerous combination of probiotics to enhance lactic acid production while simultaneously increasing the amount of carbohydrate for microbial fermentation.

Conclusions

The problems of acute D-lactic acidosis are well-understood in ruminants and horses but the characteristics and adverse side effects of acidic gut syndrome are not yet recognised in animal production or human nutrition. It is possible that a closer study of acidic gut syndrome through its effects on microbes and on the gut wall will help us to understand a range of production and health problems which are well described but for which no cause is known. The variability in the types of carbohydrates and the wide range of factors which affect their patterns of intake and passage to parts of the digestive tract where fermentation occurs have made it difficult to identify and understand the problem of fermentative acidosis as a potential disease condition.

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